REMARKS/ARGUMENTS

I. Status of the Claims

With the entry of this amendment, claims 1, 2, 4-18, and 21-29 are pending. Claims 1, 2 and 4-9, and 11-16 have been amended. Claims 21 to 29 are new. Support for amended claims 1 and 11 and new claims 21 to 29 can be found throughout the specification, and, for example, page 21, l. 29 to page 22, l. 33. Support for amended claims 1, 2 and 4-16 can be found throughout the specification and, for example, on page 5, l. 18-22. Support for amended claim 16 can be found throughout the specification and, for example, on page 26, l. 15-19. Claims 19-20 are withdrawn without prejudice to pursuing the claims in a continuing application. Claim 10 has been cancelled and the limitation of claim 10 incorporated into amended claim 1. Claim amendments are for purposes of improved clarity or consistency of claim language unless otherwise noted. No claim amendment should be construed as an acquiescence in any ground of rejection. No new matter has been added by this amendment.

Claims 1, 11, 12, and 13 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 15-18 have been rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable a method of inhibiting the expression of vitamin D nuclear receptor in cells *(in vivo)* or method of treating human having a disease or condition associated with vitamin D nuclear receptor. Claims 1, 2, 4, 5, 11 and 15 have been rejected under 35 USC § 102(b) as being anticipated by Hmama et al. (*Journal of Experimental Medicine*, **190**: 1583-1594, 1999). Claims 1, 6-10 and 12-14 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hmama et al. (*Journal of Experimental Medicine*, **190**:1583-1594, 1999) in

view of Baracchini et al. (U.S. Patent No. 5,801,154) and Fritz et al. (*Journal of Colloid and Interface Science*, **195**: 272-288, 1997).

Applicants thank Examiner Gibbs and Examiner LaCourciere for their time to discuss the Office Action and Amendment with Applicants' representative.

II. Election/ Restriction

The Office has acknowledged Applicants' election with traverse of Group I (claims 1-18) and SEQ ID NO: 3, in Paper No. 5.

III. Information Disclosure Statement

Applicants provide a supplemental Information Disclosure Statement with an English translation of the abstract of International Patent Document WO 01/38393, listed as reference AP in the Information Disclosure Statement for consideration.

IV. 35 U.S.C. § 112 second paragraph

Claims 1, 11, 12, and 13 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner alleges that the term "compound" in claims 1, 11, 12 and 13 is a relative term which renders the claim indefinite.

Applicants have amended claims 1, 2 and 4-9 and 11-16 to replace the term "compound" with the term "oligonucleotide" solely to advance prosecution of the application.

V. 35 U.S.C. § 112 first paragraph

Claims 15-18 have been rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. Applicants respectfully request reconsideration of this rejection, as there

is no evidence of record indicating that those skilled in the art would be unable to practice the methods ***as they are claimed.***

Enablement may be provided by "illustrative examples," *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993), and the initial burden is on the PTO to demonstrate an objective factual basis for questioning Applicants' disclosure. *Id.* However, the inquiry cannot stray from the metes and bounds of the claim language itself. *Ex parte Erlich*, 3 U.S.P.Q.2d 1011 (Pat. Off. Bd. App. 1987) (the invention that must be enabled is that defined by the claims).

As best understood, the Examiner states that the instant claims are not enabled because it is not known how much therapeutic benefit a particular compound will provide when introduced into an animal. This is evidenced by the following statement contained in the Office Action:

> "...further research is required in the art before vitamin D nuclear receptor antisense oligonucleotides can be employed *as a potential therapeutic means*." (emphasis added)
>
> "...the value of a potential antisense drug can only be judged after its *intended clinical use is known*, and quantitative information about its dose-response curve of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells." (emphasis added)

However, this statement (as well as the others related to targeting, permanence and quantity of expression of the gene in question, or immunogenicity) falls short of demonstrating that the compounds recited in the claims would not be expected to exhibit at least some level of activity. Indeed, Applicants do not claim a particular level of activity. Rather, their claims are directed to methods for simply modulating gene expression. Nothing

in the Office Action indicates that the claimed compounds will not modulate gene expression to at least some extent.

Significantly, the Examiner does not appear to assert that the claimed compounds will not have some level of activity. Instead, the rejection appears to be resurrecting a stringent requirement of **therapeutic** utility that was unambiguously rejected by the U.S. Patent and Trademark Office many years ago, see M.P.E.P. § 2107.02; *In re Sichert*, 566 F.2d 1154 (C.C.P.A. 1977) (holding that it is improper for the U.S. Patent and Trademark Office to require any showing regarding the degree of effectiveness of therapeutic inventions). Enablement requires only that the application teach how to make and use the invention without undue experimentation. See *In re Sichert,* 566 F.2d 1154 (C.C.P.A. 1977). The specification teaches a claimed method of inhibiting the expression of vitamin D receptor in cells or tissues by demonstrating that effective antisense oligonucleotides inhibit human vitamin D receptor mRNA levels in a cellular assay. These results provide sufficient data to predict that a claimed method of treating an animal having a disease or condition associated with vitamin D nuclear receptor will provide some level of inhibition of mRNA levels. See for example, p. 78-86, Table 1 on pages 83-84, and Table 2 on pages 85-86. There is no reason to believe that one skilled in the art would be required to perform any amount of undue experimentation to administer the claimed compounds to a subject and achieve some measurable effect.

When Applicants' specification is reviewed for support for claimed methods that involve methods for modulating gene expression in an animal by administering certain compounds to an animal, one finds more than ample illustrative examples to meet the enablement standard of *In re Wright, supra*. The specification describes instantly claimed

oligonucleotides that effectively inhibit expression of human vitamin D receptor mRNA levels. The specification further describes administration and dosing of the instantly claimed compounds at, for example, page 50-52. The specification further describes methods and formulations of the instantly claimed oligonucleotides, for example, as emulsions, liposomes, and penetration enhancers.

In view of the foregoing, Applicants submit that the pending claims are fully enabled, and request withdrawal of the rejection under 35 U.S.C. § 112.

VI. 35 U.S.C. § 102(b)

Claims 1, 2, 4, 5, 11 and 15 have been rejected under 35 USC § 102(b) as allegedly being anticipated by Hmama et al. (*Journal of Experimental Medicine*, **190**: 1583-1594, 1999). The Examiner alleges that the Hmama et al. reference disclose a 21-base pair phosphorothioate antisense oligonucleotide targeting the start codon of the human vitamin D nuclear receptor. Applicants traverse the rejection.

Applicants' claims, as amended, are to an oligonucleotide 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human vitamin D nuclear receptor (SEQ ID NO:3), wherein said oligonucleotide specifically hybridizes with said nucleic acid molecule encoding human vitamin D nuclear receptor and inhibits the expression of human vitamin D nuclear receptor, and wherein the oligonucleotide is a chimeric oligonucleotide. The Hmama et al. reference does not teach or disclose oligonucleotide molecules 8 to 50 nucleobases in length, targeted to a nucleic acid molecule encoding human vitamin D nuclear receptor, and wherein the oligonucleotide is a chimeric oligonucleotide. Therefore, claims 1, 2, 4, 5, 11 and 15 are novel in view of the Hmama et al. reference.

The rejection of claims 1, 2, 4, 5, 11 and 15 under 35 U.S.C. § 102(b) has been overcome. Therefore, Applicants respectfully request that the rejection of claims 1, 2, 4, 5, 11 and 15 be withdrawn.

VII. 35 U.S.C. § 103(a)

Claims 1, 6-10, and 12-14 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hmama et al. (*Journal of Experimental Medicine*, **190**:1583-1594, 1999) in view of Baracchini et al. (U.S. Patent No. 5,801,154) and Fritz et al. (*Journal of Colloid and Interface Science*, **195**: 272-288, 1997). Applicants traverse the rejection.

When applying 35 U.S.C. § 103, the following tenets of patent law apply:

> (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (D) Reasonable expectation of success is the standard with which obviousness is determined.
> *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

Applicants' claims, as amended, are to an oligonucleotide 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human vitamin D nuclear receptor (SEQ ID NO:3), wherein said oligonucleotide specifically hybridizes with said nucleic acid molecule encoding human vitamin D nuclear receptor and inhibits the expression of human vitamin D nuclear receptor, and wherein the oligonucleotide is a chimeric oligonucleotide. The Examiner states that the Hmama et al. reference discloses a 21-base pair phosphorothioate antisense oligonucleotide targeting the start codon of the human vitamin D nuclear receptor. The Baracchini et al. reference allegedly discloses a modified or substituted oligonucleotides. The Fritz et al. reference allegedly discloses a composition comprising an antisense

oligonucleotide and a pharmaceutically acceptable carrier or diluent comprising a colloidal dispersion system. The Hmama et al. reference in view of the Baracchini et al. and Fritz et al. references do not teach or disclose oligonucleotide molecules 8 to 50 nucleobases in length, targeted to a nucleic acid molecule encoding human vitamin D nuclear receptor, and wherein the oligonucleotide is a chimeric oligonucleotide. Furthermore, the references when combined, do not provide a reasonable expectation of success to obtain the claimed chimeric oligonucleotide. Therefore, claims 1, 2, 4, 5, 11 and 15 are patentable over the Hmama et al. reference in view of the Baracchini et al. and the Fritz et al. references.

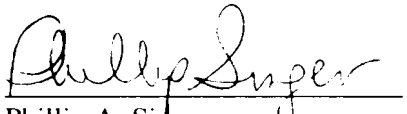
The rejection of claims 1, 2, 4, 5, 11 and 15 under 35 U.S.C. § 103(a) has been overcome. Therefore, Applicants respectfully request that the rejection of claims 1, 2, 4, 5, 11 and 15 be withdrawn.

VIII. Conclusion

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-332-1380.

Date: September 12, 2003



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